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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,097	09/10/2003	Rainer Naeff	CCS-202-CON	4324

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/04/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/659,097	NAEFF ET AL.	
	Examiner	Art Unit	
	GOLLAMUDI S. KISHORE	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 12-14-10 is acknowledged.

Claims included in the prosecution are 15-16 and 19-23.

Upon consideration, the 112 rejections are withdrawn.

Claim Rejections - 35 U.S.C. § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 15-16 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over either JP 08 231417 or Maitani (J. of Pharmaceutical Sciences, 1996) by themselves in view of JP 61097229; ***OR*** JP 08 231417 in view of Collins (5,874,075) and further in view of JP 61097229 (all are of record).

JP 147 and Maitani disclose liposomes containing erythropoietin. The liposome lipids include synthetic lecithin and cholesterol and phosphate buffer (note the abstract of JP; abstract and Experimental section in Maitani). As well known in the art, liposomal compositions have two aqueous compartments, one within the bilayer and the other

outside the bilayer and the hydrophilic compounds are generally added to the hydrating medium such that part of it is encapsulated in the aqueous compartment within the liposome and unencapsulated active agent is in the outer aqueous medium. In both JP and Maitani, the unencapsulated erythropoietin is removed by filtration. However, it would have been obvious to one of ordinary skill in the art not to remove the compound is such is desired.

Collins as pointed out before teaches liposomal compositions containing hematopoietic factors including erythropoietin (col. 7, lines 44-50 and examples). The phospholipids include dipalmitoylphosphatidic acid (col. 4, lines 29-45). The liposomes further contain PEG (stabilizer) and a phosphate buffer. The compositions further contain preservatives (col. 12, line 52). The method of preparation involves incubating the liposomes with the hematopoietic factor (Example 1). According to Collins, such an attachment stabilizes the proteins such as erythropoietin. One of ordinary skill in the art would be motivated not to remove the external erythropoietin since Collins teaches that erythropoietin outside the liposomes stabilizes such proteins. JP, Maitani and Collins do not teach the inclusion of glycine in the liposomal formulations. Such an inclusion however, would have been obvious to one of ordinary skill in the art in view of JP 229, which teaches that glycine is a stabilizer for erythropoietin (note the abstract). To include preservatives such as BHA or BHT would have been obvious to one of ordinary skill in the art since these are art known preservatives and antioxidants.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that JP and Maitani require the use of reverse-phase evaporation in

the preparation of the composition and the presently claimed invention does not claim this technique or products by this technique. This argument is not persuasive. As pointed out before instant claims are composition claims and not a method of preparation claims. As is well known in the art there are several methods of preparation of liposomes and the reference of Collins clearly teaches the classical method of preparation of liposomes by hydrating the lipid film with an aqueous medium (Example 1). Furthermore, EP 0 253 619 already of record shows the preparation of liposomes by ethanol injection into an aqueous medium under pressure in a high speed homogenizer (see abstract). Applicant argues that in JP the non-encapsulated EPO is removed by filtration and in fact the examiner admits to this. The examiner points out once again that one of ordinary skill in the art would be motivated to not to remove EPO which is outside the liposomes, in the external aqueous medium because Collins teaches proteins such as EPO are stabilized when they are outside the liposomes (that is in the external aqueous medium). Applicant argues that the examiner admits that JP does not teach the use of glycine. However, JP 229 teaches that glycine is a stabilizer for EPO and therefore, one of ordinary skill in the art would be motivated to use glycine in JP 417. Applicant's arguments that the examiner provided no rationale or merit based analysis as to why one of ordinary skill in the art would rely on JP 417 as a teaching or suggestion for not removing the non-encapsulated EPO. This argument is not persuasive since the purpose in JP is to totally encapsulate EPO for the intended purpose and one of ordinary skill in the art would not undertake an additional step of filtration if removal of outside EPO is not necessary. Applicant's arguments regarding

Maitani are similar to those of JP 417 and therefore, the same reasoning is applicable. Applicant argues that as stated in the specification, the use of REV to encapsulate EPO suffers high loss of unencapsulated EPO, which is undesirable and expensive and therefore, there would be no motivation for one of ordinary skill in the art to want to waste expensive free EOP in the practice of 417 and Maitani where REV is used to drive the encapsulation of EPO. This argument is not persuasive. Liposomes are sustained release vehicles for drugs and the purpose of encapsulation of any drug is for this purpose. If the active agent (EPO) is present only in the aqueous medium outside the liposomes, its effect would be similar to the effect observed using free EPO. Furthermore, JP 229 clearly teaches that glycine is a stabilizing agent and therefore, one of ordinary skill in the art would be motivated not to remove the unencapsulated EPO since glycine is stabilizing even the unencapsulated EPO. Applicant has not shown any unexpected results by using a liposomal composition wherein EPO is present only outside the liposomes.

Applicant's arguments that Collins does not remedy the shortcomings of the 417 reference because Collins fails to teach EPO being dispersed within the aqueous phase and not within a liposome of the lipidic phase. According to applicant, Collins does not specifically teach EPO as part of any specific liposomal based parenteral composition and Collins mentions EPO as part of a larger group of compounds that could be considered for use in the Collins invention. Further according applicant Collins brief mentioning of EPO as member of a large group is nothing more than an invitation to experiment. This argument is not persuasive since Collins teaches limited number of

hematopoietic factors which includes erythropoietin and Collins clearly states that if the hematopoietic factor is outside the liposomes it is stabilized. Applicant further argues that Collins requires very specific modifications for bonding/bridging select compounds to incorporate those select compounds into the membrane of the liposomes which requires protein modification and point out col. 8, lines 8-25 of Collins. This argument is not persuasive since what is taught in Example 1 of Collins is mixing of hematopoietic factor itself (G-CSF) and not modified G-CSF.

Applicant argues that in Collins the G-CSF is incorporated into the membrane and not dispersal in the aqueous medium. This argument is not persuasive since Example 1 in Collins shows the incubation of liposomes with an aqueous solution of the protein and if EPO attaches to the liposomal surface by some interactions, then EPO would behave the same way in instant invention also. In response, applicant argues that office offers no scientific rationale regarding this point. This argument is not persuasive since the examples in instant specification which show incubation of EPO with the liposomes provide the scientific rationale. By similar incubation as taught in Collins, applicant is claiming that EPO is dispersed in the aqueous phase which is outside the liposomes. If EPO remains dispersed in the aqueous phase with such an incubation, one would expect the same results in Collins also.

Applicant's arguments that JP 229 discloses glycine as stabilizer for EPO but silent in EPO being dispersed within the aqueous phase and accordingly does not cure the deficiency of JP 417 and Maitani are not persuasive since this reference is added to show that glycine offers stability to EPO in aqueous solutions. Furthermore, as noted

above, applicants themselves state that that their unexpected discovery is that the liposomal EPO compositions prepared under mild conditions exhibit improved stability. From the teachings of JP 229 one could argue that the improved stability observed by applicants is due to the stability offered by glycine and is to be expected.

3. Claims 15-16 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins (5,874,075) in view of JP 61097229 (all are of record).

Collins as pointed out before teaches liposomal compositions containing hematopoietic factors including erythropoietin (col. 7, lines 44-50 and examples). The phospholipids include dipalmitoylphosphatidic acid (col. 4, lines 29-45). The liposomes further contain PEG (stabilizer) and a phosphate buffer. The method of preparation involves incubating the liposomes with the hematopoietic factor (Example 1). According to Collins, such an attachment stabilizes the proteins such as erythropoietin.

Collins does not teach the inclusion of glycine in the liposomal formulations. Such an inclusion however, would have been obvious to one of ordinary skill in the art in view of JP 229, which teaches that glycine is a stabilizer for erythropoietin (note the abstract).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Collins teaches a broad genus of the compounds with little to know guidance regarding members of the genus except for G-CSF and that the Office is merely picking and choosing from a broad genus of compounds in an attempt to anticipate the presently claimed invention.

This argument is not persuasive since this is a 103 rejection and Collins is suggestive of the use of erythropoietin in the liposomal preparation. Collins provides guidance for the preparation of liposomes and teaches the incubation of the liposomes with G-CSF just as in instant invention and one of ordinary skill in the art therefore, would be motivated to use any hematopoietic factor including erythropoietin with the expectation of obtaining at least similar results as observed with G-CSF.

4. Claims 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over either JP 08 231417 or Maitani (J. of Pharmaceutical Sciences, 1996) by themselves in view of JP 61097229; ***OR*** JP 08 231417 in view of Collins (5,874,075) and further in view of JP 61097229; ***OR*** Collins (5,874,075) in view of JP 61097229 all of them as set forth above, further in view of Benz (6,214,388).

The teachings of JP 417, Maitani, JP 229 and Collins have been discussed above. What is lacking in these references is the explicit teaching of the inclusion of an antioxidant and a complexing agent.

Benz while disclosing liposome formulations for the delivery of compounds such as erythropoietin teaches the inclusion of antioxidants, alpha tocopherol and iron specific chelators (col. 13, lines 38-39; col. 18, lines 60-65) for the protection of lipids.

The inclusion of preservatives, antioxidants and chelators would have been obvious to one of ordinary skill in the art since these are lipid protecting agents as taught by Benz.

Applicant argues that one of ordinary skill in the art would not be able to cure the deficiencies of Collins by looking to JP 229 since JP 229 does not teach a liposomal-based dispersion. This argument is not persuasive since JP specifically teaches that glycine is a stabilizer for erythropoietin. Therefore, one of ordinary skill in the art would recognize that glycine will stabilize erythropoietin whether it is in a liposomal preparation or in a non-liposomal preparation and applicant has not shown that to be otherwise.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK